



(19)

Europäisches Patentamt

European Patent Office

## Office européen des brevets

(11)

EP 1 046 395 A1



(12)

# EUROPEAN PATENT APPLICATION

(43) Date of publication:  
**25.10.2000 Bulletin 2000/43**

(51) Int. Cl.<sup>7</sup>: **A61K 9/70, A61K 31/727**  
// (A61K31/727, 31:196)

(21) Application number: 00107835.1

(22) Date of filing: 12.04.2000

(84) Designated Contracting States:  
**AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU  
MC NL PT SE**  
Designated Extension States:  
**AL LT LV MK RO SI**

(30) Priority: 21.04.1999 IT MI990834

(71) Applicant: **ALTERGON S.A.**  
**CH-6901 Lugano (CH)**

(72) Inventors:

- **Donati, Elisabetta**  
22020 Cavallasca (CO) (IT)
- **Rapaport, Irina**  
6821 Rovio (CH)

(74) Representative:

**Gervasi, Gemma, Dr.  
NOTARBARTOLO & GERVASI Srl,  
Corso di Porta Vittoria, 9  
20122 Milano (IT)**

**(54) Plaster for topical use containing heparin and diclofenac**

(57) Plaster for topical use having an analgesic activity and at the same time being able to re-absorb haematomas, comprising:

a substrate layer;  
an adhesive layer in the form of a hydrogel matrix containing a pharmaceutically acceptable diclofenac salt, heparin or a heparinoid;  
a protective film which can be removed at the moment of use.

**BEST AVAILABLE COPY**

EP 1 046 395 A1

**Description****Scope of invention**

5 [0001] Plaster for topical use having an analgesic activity and being able to re-absorb haematomas, containing diclofenac in association with heparin or a heparinoid.

**State of the art**

10 [0002] Known and available on the market are creams for topical use with a base of heparinoids, possibly in association with hyaluronidase, for re-absorption of haematomas and ecchymoses.

[0003] Though remarkably effective, these creams involve a number of drawbacks. In fact, they do not present a more specific analgesic activity, which would be particularly necessary in the case of serious ecchymoses.

15 [0004] In addition, the creams, the application of which involves first spreading the cream, and subsequently rubbing or gentle massaging on the area affected, do not enable uniform dosing of the active principle from one application to the next. In addition, with this type of formulation it is not possible to control in any way the release of active principle; consequently, these formulations must be applied on the area affected at least twice a day, with considerable inconvenience, in that they necessarily leave greasy residue on the skin.

20 [0005] In the European Patent Application EP-A-621263, a plaster is described containing as active principle only diclofenac in the form of a pharmaceutically acceptable salt with an alicyclic organic base.

[0006] This type of plaster represents an alternative system to oral administration of diclofenac, and administration which, as is known, presents considerable undesirable effects at the gastric level.

**Summary of invention**

25 [0007] The applicant has now discovered a plaster containing heparin or heparinoids in association with diclofenac or one of its salts that is pharmaceutically acceptable for topical use, which does not present the drawbacks of the cream compositions that are known for the same type of use.

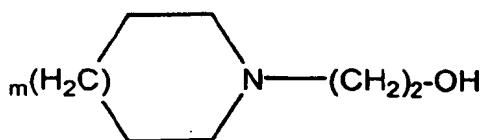
[0008] This plaster in particular comprises:

30 a) a substrate layer;  
 b) an adhesive layer in the form of a hydrogel matrix in which the above-mentioned active principles are dispersed;  
 c) a protective film which can be removed at the moment of use.

**Detailed description of invention**

35 [0009] In the plaster according to the present invention, diclofenac is generally present in the form of a pharmaceutically acceptable salt, and preferably it is a salt with a heterocyclic amine of general formula:

40



45

where  $m$  is 0 or 1.

[0010] According to a particularly preferred embodiment, the heterocyclic amine is *N*-hydroxyethyl pyrrolidine (epolamine).

[0011] The diclofenac salt is contained in the plaster according to the present invention in concentrations generally ranging from 0.1 to 5 wt%, preferably in concentrations of between 0.3 and 3 wt% with respect to the total weight of the composition used for the preparation of the hydrogel matrix.

[0012] According to a particularly preferred embodiment, the concentration of the diclofenac salt is 1.3 wt% with respect to the total weight of the composition used for the preparation of the hydrogel matrix.

[0013] When the plaster according to the present invention contains a heparinoid, the latter preferably presents a molecular weight of between 5,000 and 30,000 DA. The heparin or heparinoid is present in concentrations such that its total quantity in the plaster is between 0.05 and 1%, which corresponds respectively to a concentration range of

between 1,400 and 28,000 IU/plaster (100-2,000 IU/g matrix).

[0014] According to a particularly preferred embodiment, heparin is contained in concentrations such that the corresponding content is 5600 IU per plaster. It is advisable that the composition used for preparing the hydrogel matrix should present pH values of between 7.2 and 9, preferably of between 7.5 and 8.5. At pH values lower than 7.2, the diclofenac crystals that are insoluble in water precipitate; values higher than 9 may cause irritation of the skin. To adjust the pH of the hydrogel composition, any organic or inorganic acid, or any organic or inorganic base may be used, without any particular limitation. The concentration of the above-mentioned acid or base is not critical either and may vary according to the pH value that the hydrogel composition reaches.

[0015] In addition to the aforementioned active principles, the hydrogel matrix further contains thickening agents, wetting agents, fillers, preservatives, cross-linking agents, surfactants, stabilizers, etc.

[0016] Preferably, the composition used for the preparation of the hydrogel matrix contains as thickening agents the following: polyacrylic acid, sodium polyacrylate, sodium carboxymethyl cellulose, polyvinyl alcohol, polyvinyl pyrrolidone, gelatine or corresponding mixtures. The concentration of the above additives is generally between 3 and 30 wt%, preferably between 5 and 20 wt%. If the concentration is lower than 3 wt%, the viscosity of the composition is too low, so that the composition comes out of the plaster and remains on the skin once the plaster is applied; on the other hand, if the concentration is too high, it is not very workable.

[0017] According to a particularly preferred embodiment, the thickening agents are a mixture consisting of the following: gelatine, polyvinyl pyrrolidone, sodium polyacrylate, and sodium carboxymethyl cellulose in a total concentration of 9 wt% with respect to the total weight of the hydrogel matrix.

[0018] The hydrogel matrix of the plaster according to the present invention preferably comprises at least one wetting agent chosen from among glycerol, propylene glycol, polyethylene glycol, 1,3-butanediol, and an aqueous solution of D-sorbitol, preferably in a concentration of 70 wt%.

[0019] The concentration of the said wetting agents in the composition used for the preparation of the hydrogel matrix according to the present invention is between 5 and 70 wt%, preferably between 10 and 60 wt% with respect to the total weight of the composition used for the preparation of the hydrogel matrix.

[0020] If the quantity of wetting agent is lower than 5%, the wetting effect is not sufficient and the composition dries quickly; if, instead, the quantity of wetting agent is higher than 70%, mixing of the components is difficult.

[0021] The cross-linking agent is preferably an aluminium or calcium compound present in the composition used for the preparation of the hydrogel matrix in a concentration of between 0.01 and 3.0 wt%. If the quantity of this additive is lower than 0.01 wt%, cross-linking is insufficient, so that the resistance to heat of the hydrogel matrix is reduced; consequently, two drawbacks may occur, either during storage or during application: during storage, the composition is too fluid and comes out of the plaster in the sterile container of the latter; when the plaster is applied, the composition leaves a residue on the skin. When the concentration of the cross-linking agent is higher than 3%, the rate of cross-linking is too high and consequently the viscosity of the composition used for the preparation of hydrogel matrix increases, so that the corresponding workability decreases.

[0022] As a filler, one of the following, for instance, may be used: kaolin, titanium dioxide, bentonite, or mixtures of the said compounds.

[0023] As a preservative, the hydrogel matrix that is the subject of the present invention may contain either preservatives of a conventional type, such as the esters of *para*-alkyloxy benzoic acid, for example Nipagin and Nipasol, or sorbic acid. The hydrogel matrix may possibly contain a surfactant, such as a polyoxyethylene sorbitan ester (Tween 80) and a stabilizer, such as sodium ethylenediamine tetraacetate.

[0024] As far as the substrate layer is concerned, any material usually employed for this purpose may be used, such as fabric, non-woven fabric, paper, plastic film and corresponding laminates.

[0025] As regards the removable protective film, this may be of a conventional type, for instance, siliconized paper, or may be made of a plastic material, such as polyethylene, polyethylene terephthalate, or polyvinyl chloride.

[0026] The present plaster is prepared according to conventional methods which, in particular, envisage the following fundamental stages:

mixing of the various components of the composition used for the preparation of the hydrogel matrix,  
50 co-extrusion of the hydrogel matrix between the substrate layer and the removable protective film.

[0027] The mixing phase is in particular conducted in the following stages:

55 1-A) mixing of one part of water with the filler and with part both of the cross-linking agent and of the thickening agent;

1-B) subsequent addition to the mixture obtained in stage (1-A) of further thickening agents;

1-C) addition to the mixture obtained in stage (1-B) of preservatives, a stabilizer, a pH adjuster, as well as of the remaining part of the cross-linking agent and thickening and wetting agents;

BEST AVAILABLE COPY

1-D) addition to the mixture obtained in stage (1-C) of the pharmaceutically acceptable diclofenac salt;  
 1-E) addition to the mixture obtained in stage (1-D) of the heparin or heparinoid. To provide a non-limiting illustration, an example is given of preparation of the hydrogel matrix used as adhesive layer of the plaster according to the present invention.

5

COMPONENTS	% (p/p)
DIEP	1.3
Sodium heparin 198 IU/mg	0.202 (5600 IU) per plaster
Gelatine	2.0
Polyvinyl pyrrolidone	2.0
Nipagin	0.1
Nipasol	0.05
Propylene glycol	3.0
Tween 80	0.2
Kaolin	3.0
Titanium dioxide	0.5
Sorbitol	40.0
EDTA Na	0.12
tartaric acid	0.5
Aluminium glycinate	0.3
Sodium polyacrylate	4.0
Sodium carboxymethyl cellulose	3.0
Butylene glycol	10.0
Water	29.73

10

15

20

25

30

35

**[0028]** One part of water, kaolin, titanium dioxide and 70% sorbitol is added; to this is added, in the form of an aqueous solution, one half of the quantity of dihydroxy aluminium glycinate, sodium polyacrylate, sodium carboxymethyl cellulose, and 1,3-butanediol. Everything is mixed by stirring.

**[0029]** To the mixture thus obtained is added an aqueous mixture of gelatine and polyvinyl pyrrolidone, an aqueous solution containing Nipagin, Nipasol, NaEDTA, tartaric acid, and finally an aqueous solution consisting of the remaining part of aluminium glycinate, 1,3-butanediol, sodium carboxymethyl cellulose and sodium polyacrylate, and subsequently the product is mixed under stirring.

**[0030]** To the mixture thus obtained, finally the active principles are added; first, a solution is added of the diclofenac salt with *N*-hydroxyethyl pyrrolidine (DIEP), and finally a heparin aqueous solution, to obtain the composition given in the table above, which is subsequently extruded.

### Claims

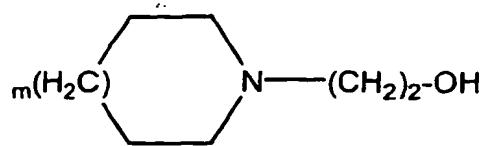
**50 1.** Plaster for topical use having an analgesic activity and at the same time being able to re-absorb haematomas, comprising:

- a substrate layer;
- an adhesive layer in the form of a hydrogel matrix containing a pharmaceutically acceptable diclofenac salt and heparin or a heparinoid;
- a protective film which can be removed at the moment of use.

**2.** The plaster according to Claim 1, characterized in that the diclofenac salt is in the form of a salt with an alicyclic

55

amine of general formula:



10 in which m is 0 or 1.

3. The plaster according to Claim 1 or Claim 2, characterized in that the diclofenac salt used in the plaster according to the present invention is *N*-hydroxyethyl pyrrolidine (epolamine).

15 4. The plaster according to any one of Claims 1-3, characterized in that the diclofenac salt is contained in concentrations of between 0.1 and 5 wt% with respect to the total weight of the compositions used for the preparation of the hydrogel matrix.

20 5. The plaster according to Claim 4, characterized in that the said concentration is between 0.3 and 3 wt% with respect to the total weight of the composition used for the preparation of the matrix.

25 6. The plaster according to any one of Claims 1-5, in which heparin or heparinoid is contained in such concentrations in the composition used for the preparation of the hydrogel matrix that the total content of sodium heparin or heparinoid contained in the plaster is between 0.05 and 1 wt% with respect to the total weight of the hydrogel matrix.

35 7. The plaster according to any one of Claims 1-6, characterized in that the pH of the composition used for the preparation of the hydrogel matrix is between 7.2 and 9.

30 8. The plaster according to Claim 7, characterized in that the said pH is between 7.5 and 8.5.

9. The plaster according to any one of Claims 1-8, characterized in that the composition used for the preparation of the hydrogel matrix contains at least one thickening agent chosen from among the group consisting of polyacrylic acid, sodium polyacrylate, sodium carboxymethyl cellulose, polyvinyl alcohol, polyvinyl pyrrolidone, gelatine or corresponding mixtures.

40 10. The plaster according to Claim 9, characterized in that the concentration of the said thickening agent in the composition used for the preparation of the hydrogel matrix is between 3 and 30 wt%.

45 11. The plaster according to Claim 10, characterized in that the said concentration is between 5 and 20 wt% with respect to the total weight of the composition used for the preparation of the hydrogel matrix.

12. The plaster according to any one of Claims 1-12, characterized in that the composition used for the preparation of the hydrogel matrix contains at least one wetting agent chosen from among the group consisting of glycerol, propylene glycol, polyethylene glycol, 1,3-butanediol, and an aqueous solution of D-sorbitol, preferably in a concentration of 70%.

50 13. The plaster according to Claim 12, characterized in that the concentration of wetting agents is between 10 and 60 wt% with respect to the total weight of the composition used for the preparation of the hydrogel matrix.

14. The plaster according to any one of Claims 1-13, characterized in that the composition used for the preparation of the hydrogel matrix contains at least one cross-linking agent at concentrations of between 0.01 and 3 wt% with respect to the total weight of the composition.

55

**BEST AVAILABLE COPY**



European Patent  
Office

## EUROPEAN SEARCH REPORT

Application Number  
EP 00 10 7835

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.)
D,A	EP 0 621 263 A (TEIKOKU SEIYAKU KK ;ALTERGON SA (CH)) 26 October 1994 (1994-10-26) * page 2, line 49 – page 3, line 12; claims; examples *	1-14	A61K9/70 A61K31/727 //(A61K31/727, 31:196)
A	US 4 855 142 A (FANKHAUSER PETER ET AL) 8 August 1989 (1989-08-08) * column 2, line 5 – line 32; examples *	1-14	
TECHNICAL FIELDS SEARCHED (Int.Cl.)			
A61K			
The present search report has been drawn up for all claims			
Place of search	Date of completion of the search	Examiner	
THE HAGUE	30 June 2000	Epskamp, S	
CATEGORY OF CITED DOCUMENTS			
X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document			
T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document			

ANNEX TO THE EUROPEAN SEARCH REPORT  
ON EUROPEAN PATENT APPLICATION NO.

EP 00 10 7835

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on. The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

30-06-2000

Patent document cited in search report		Publication date		Patent family member(s)	Publication date
EP 0621263	A	26-10-1994		JP 6305958 A CA 2121065 A KR 123932 B US 5607690 A ZA 9402637 A	01-11-1994 24-10-1994 24-11-1997 04-03-1997 07-11-1994
US 4855142	A	08-08-1989		AU 1235088 A DK 100488 A EP 0283434 A JP 63227522 A PT 86828 A, B	01-09-1988 28-08-1988 21-09-1988 21-09-1988 01-03-1988

BEST AVAILABLE COPY

This Page Blank (uspto)